

# Methodological challenges in female-controlled methods of prevention of of HIV

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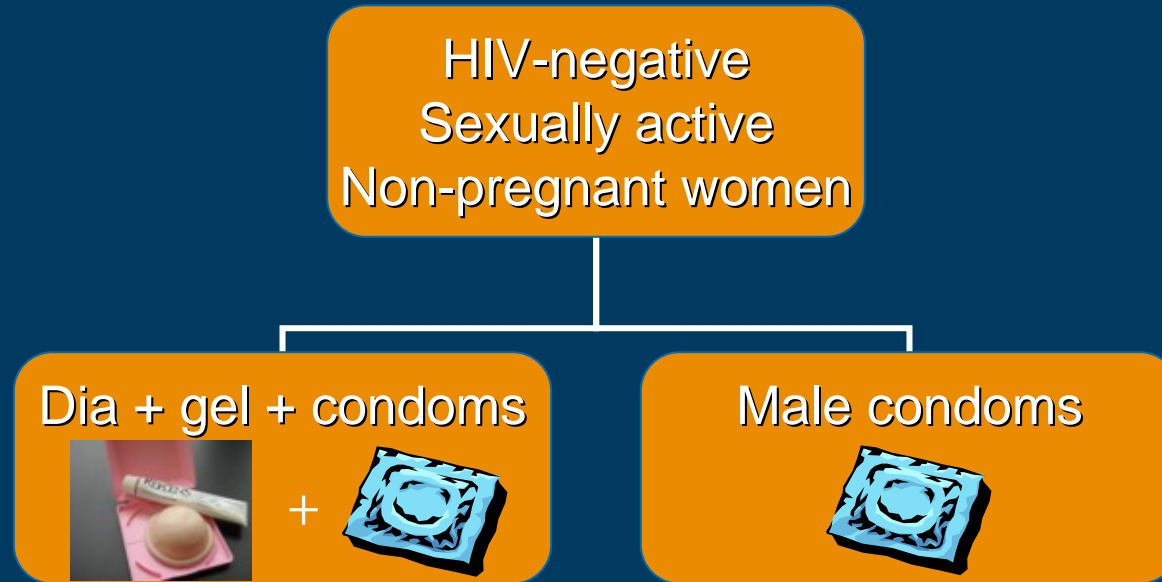
# Female-controlled methods:

Microbicides, *diaphragms*, female condoms

- Review results from MIRA (Methods for Improving Reproductive Health in Africa)
- Consider methodological challenges
- Present future considerations

# MIRA Study Design

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- All women received risk reduction counseling, free male condoms and diagnosis and treatment of curable STIs
- Women were followed quarterly for 12-24 months

# MIRA Trial Sites



**Total n = 5045**

**UZ-UCSF**

**Harare, Zimbabwe  
n=2502**

**PHRU**

**Soweto, South Africa  
n=1028**

**MRC**

**Durban, South Africa  
n=1515**

# MIRA Results from ITT (n=4948)

HIV	Incidence rate	Relative Hazard (95% CI)
<b>All Sites</b>	<b>4.0</b>	<b>1.05 (0.84 – 1.32)</b>
Harare	2.7	1.20 (0.83 – 1.74)
Durban	6.8	0.95 (0.69 – 1.31)
Johannesburg	3.4	1.05 (0.60 – 1.87)

# MIRA bottom line

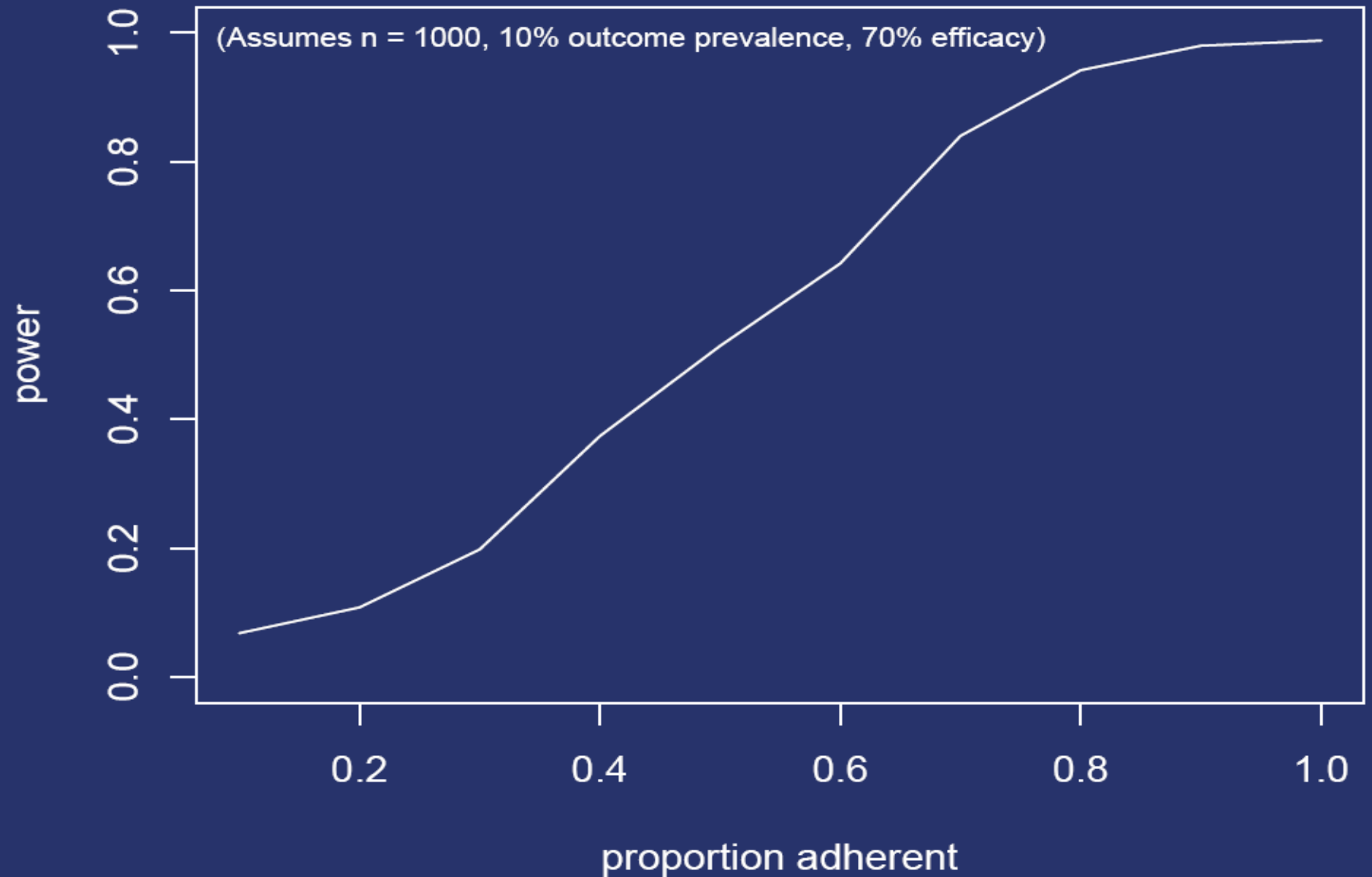
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In the context of a comprehensive HIV prevention package offered to all participants, the trial found *no additional protective benefit against HIV infection* from providing the diaphragm plus lubricant in the intervention arm.

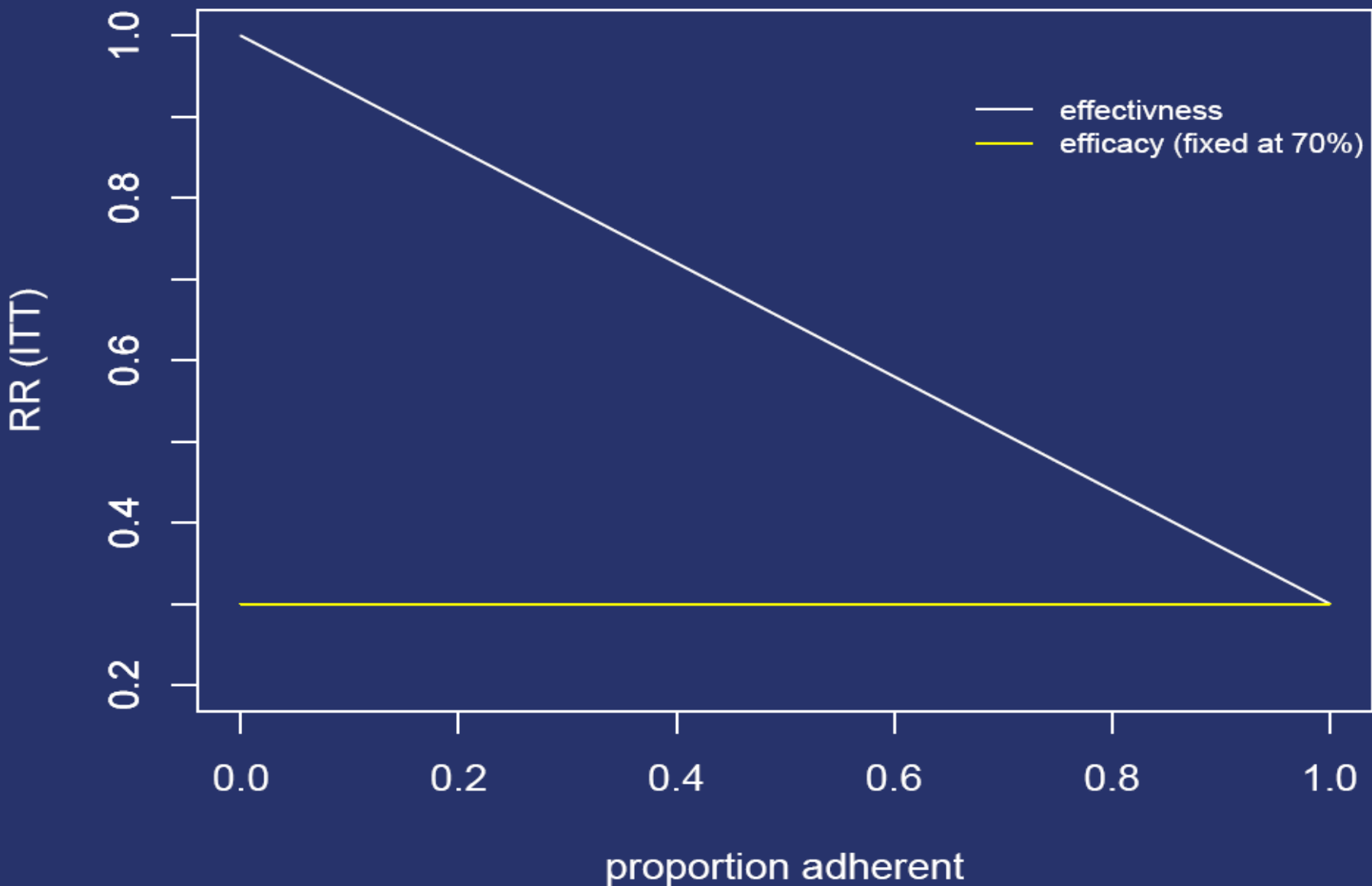
# Previously recognized challenges in HIV microbicide trials

Challenge	Expected in MIRA	Observed in MIRA
1. Low HIV incidence	4.0%	4.0%
2. High pregnancy rates	Not pre-specified	13% annual incidence
3. High retention rates	$\geq 90\%$	92.5%
4. <i>Suboptimal product adherence:</i>	<i>80% of sex acts</i>	<i>73% at last sex; 58% “always”</i>
5. <b>Multi component intervention</b>		

# Relationship between power and adherence in an ITT analysis



# Relationship between effectiveness and adherence in an ITT analysis



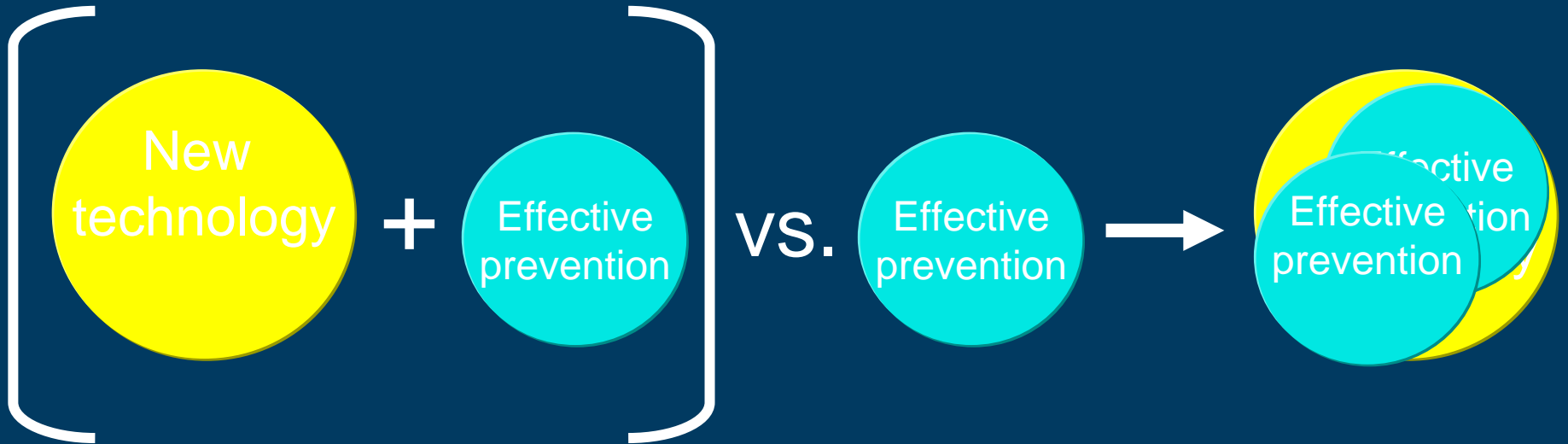
# Evaluating multi-component technologies

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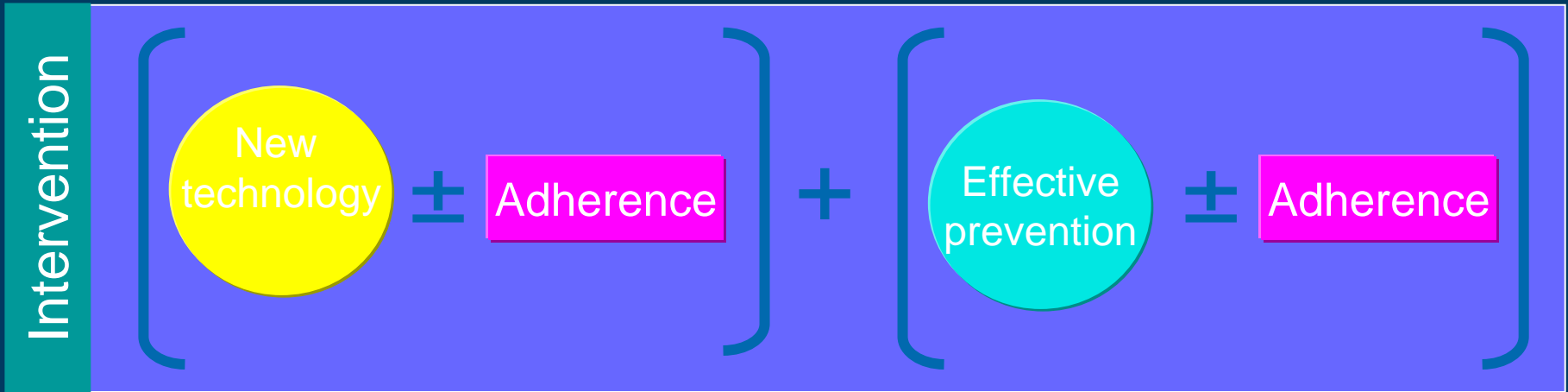
Intervention

Control

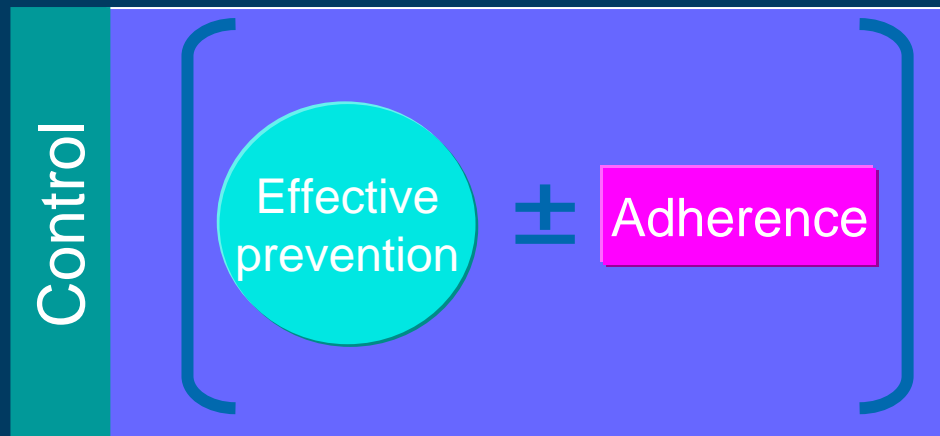
Attributable fraction



# Adherence to multi-component interventions

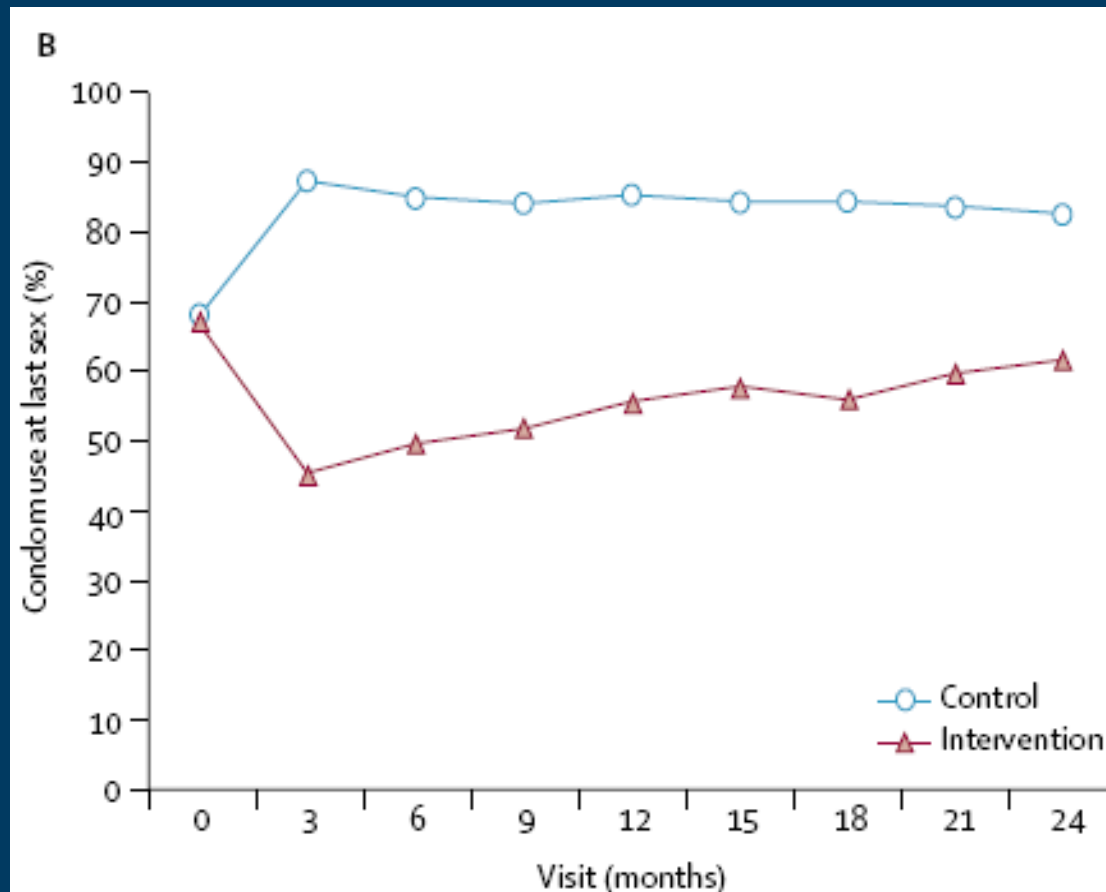


VS.



# Differential condom use in MIRA, non-independence

Figure 3. Proportion of women reporting condom use at last sex, by visit



# Effect of adherence + *differential condom use*

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Post-trial simulations, with levels of diaphragm and condom use equivalent to that observed in MIRA:

- 70% diaphragm use (in intervention arm)
- 85% condom use in the control arm
- 50% condom use in the intervention arm



Power to detect a 33% reduction in incidence is  $< 25\%$

# Effect of dependence between product adherence & condom use in placebo-controlled studies

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Assume that all adherent participants use condoms in both arms and condoms are 100% protective:

		<u>Product</u>	
		Condom use	
		Yes	No
Adhere	Yes	350	0
	No	50	100
		400	100

		<u>Placebo</u>	
		Condom use	
		Yes	No
Adhere	Yes	350	0
	No	50	100
		400	100

# Effect of dependence between adherence & condom use in placebo-controlled studies

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ITT analysis:

	Product	Placebo
HIV+	10	10
HIV-	490	490
	500	500

$RR = [(10/500)/(10/500)] = 1.0$  (no effect of treatment)

Conclusion: No information about tx effects because all adherent individuals also use condoms.

# Future Considerations

Reconsider the research question.  
Compared to what??  
MIRA could not assess...

- Whether a diaphragm is as good as a condom
- Whether a diaphragm is better than nothing

# Most vulnerable women

- Majority of women are at risk because their male partners do not use condoms
- Current trial results may not be generalizable to them
- Condom use during the study may not reflect “real life”

# Appropriate comparison: sustainability of high levels of condom use beyond the trial

- Survey of participants enrolled in an RCT of N-in Cameroon 14 months after study participation
- Attributable to a change in behavior or in reporting?

	During study	Post-study
% of acts with condoms	82 - 84	57
% of ppts reporting consistent condom use	64 - 67	35

# Inextricable relationship between adherence and effectiveness

**Adherence**

**Effectiveness**



# Challenges in measurement of adherence:

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- Use and compliance are unobserved and self-reported
- Self-reports are subject to bias
  - Social desirability
    - Value of the saying what's in the counseling message
    - Confounded by benefits of study participation
  - Recall (cant remember)
    - Think of those of us who are challenged by time sheets
  - Interviewer
    - Difficult to standardize counseling across all staff for the duration of the trial, affects adherence and its measurement

# Novel methods of self-report:

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- For self-report, Cell phones, electronic diaries, etc..
- DOP
- Innovative biological markers:
  - Markers of unprotected sex
  - Drug concentration in hair specimens
  - Drug metabolites in breath specimens
  - Devices (barriers, applicators) with computer chips or dye that register use (body heat, pH)

# Study Designs that optimize adherence and refocus the research question

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- Pre-randomization study (run-in)
  - Select non-condom users (e.g. sex workers)
  - Select good product adherers (using biomarkers or predictors of use)
- Post randomization: adaptive designs
- Nature of control arm
  - Reconsider standards of condom counseling
    - Community standard vs. enhanced counseling?
    - Uncouple condom counseling from intervention protocols: e.g. as part of VCT prior to enrollment?
  - Head-on comparison of intervention to condom (true equivalence)?

# Alternative methods of analyses

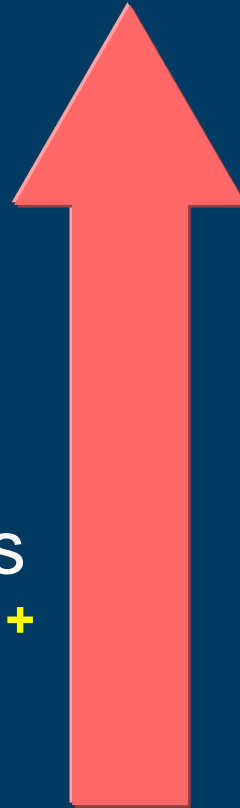
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Moving beyond traditional intent-to-treat (ITT):

- Direct effects - uses counterfactuals that model estimated effects of the intervention while maintaining randomization and controlling for causal intermediates
  - For example, analyze data as if all women did (or did not) use condoms or diaphragms
  - Allows evaluation of the direct effects of the intervention

# Making the best of available evidence

- Male circumcision
- STD tx for HIV
- Male condom\* +
- Female condom\* +
- Abstinence +
- Reducing # of sex partners (absolute and concurrent) +
- Postponing sexual debut +



More evidence

Less evidence

\* Effectiveness based on 100% use and is indirect

+ No HIV trial evidence: biological plausibility, laboratory data and evidence from observational studies

# MIRA team

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